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ESSENTIAL HYPERTENSIVE VASCULAR DISEASE: PATHOGENESIS AND PATHOPHYSIOLOGY

GERALD R. DRESLINSKI, M.D., EDWARD D. FROHLICH, M.D., FRANZ H. MESSERLI, M.D., AND FRANCIS G. DUNN, M.D.

Department of Internal Medicine
Ochsner Clinic and the Alton Ochsner Medical Foundation
New Orleans, Louisiana

MORE than 50 million Americans are said to have high blood pressure. About 95% of these patients have hypertension without known cause; they have essential hypertension. Although all hypertensive diseases share the hemodynamic hallmark of an elevated arterial pressure and an increased total peripheral resistance, they constitute anything but a homogeneous classification. Insight into therapy of these disorders has come about through understanding their hemodynamic characteristics and the interactions of the pressor and depressor mechanisms that operate in each patient.

Hemodynamics. The early phases of essential hypertension, both established and borderline, often manifest a rapid heart rate, elevated cardiac

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output, and an increased myocardial contractile state, without evidence of expanded blood volume. The normal circulating intravascular volume shifts to the cardiopulmonary area from the peripheral circulation, suggesting venular smooth muscle constriction in addition to arteriolar constriction.[1-4] Associated with increased myocardial contractility may be slightly contracted blood volume and a normal cardiac output.[5,6] As the hypertensive vascular disease process progresses in untreated patients, total peripheral resistance increases and plasma volume contracts, and the cardiopulmonary volume and cardiac output decline with this slightly diminishing venous return. Renal and splanchnic blood flows decline in parallel.[6]

Although this synopsis oversimplifies the pathologic vascular changes that occur throughout the various stages of essential hypertension, several points seem clear. Associated with the hallmark of arteriolar constriction that increases total peripheral resistance is evidence of venoconstriction and cardiac stimulation. Classically, we monitor these cardiovascular hemodynamic changes by evaluating major target organ functions: optic fundi and their vessels, the heart, and the kidneys. The functional changes reflected in these organs are manifestations of progressive systemic vascular disease secondary to sustained vasoconstriction. To understand functional changes in the target organs, one must be aware that it is the vasculature that takes the brunt both of the sustained constriction and of the elevated arterial pressure.

Systemic Vascular Disease

In 1827 Bright reported the coexistence of granular contracted kidneys and an enlarged heart. Nearly 50 years thereafter, Gull and Sutton described the pathologic changes of arteriocapillary fibrosis. Twenty-five years later, Riva-Rocci first made indirect measurements of arterial pressure. These discoveries made possible the association of the changes with elevations in blood pressure and vascular disease.[7]

The late 19th and 20th centuries saw considerable work in experimental hypertension. Methods to produce experimental hypertension and to observe the morphologic changes in the blood vessels, heart, and kidneys of laboratory animals yielded a rich harvest of knowledge of the sequential changes occurring as uncontrolled hypertensive vascular disease continues. The pathologic changes in small arterioles have been described as those of arteriosclerosis, which may be divided into two morphologic

entities. First is medial hypertrophy and degeneration, characterized structurally by increased wall-to-lumen ratio of the arterioles, mainly an increased wall thickness because the diameter of the lumen changes little. Hypertrophy of vascular smooth muscle cells reflects the increased workload imposed upon them by sustained increase in smooth muscle tone and resultant vasoconstriction. Second is intimal thickening secondary to cellular and elastic proliferation, which also occurs in response to the increased workload. As this process goes unchecked, hyalinization occurs. We should remember that these pathological alterations are produced by changes in the pressor and depressor mechanisms that actively increase the tone of the vascular smooth muscle. As noted, this diffuse systemic process eventually produces functional changes in every organ and, in particular, may be assessed in the so-called "target organs" familiar to physicians: optic fundi, heart, and kidneys.

Hypertensive Vascular Adaptations

Retinopathy. The retinal vessels are unique among the systemic and regional circulations of the human body because they are the only small vessels that can be visualized and assessed noninvasively by clinicians by physical examination, and they provide an *in vivo* index to assess the degree of vasoconstriction, severity of hypertensive disease, and coexistence of sclerosis of the arterioles.

The work of Keith, Wagener, and Barker provided the groundwork for estimating the severity and prognosis of hypertensive retinal vascular disease.[8] The American Ophthalmological Society further quantified this classification to describe progression of vascular disease by attention to the degree of tortuosity and focal or generalized narrowing of the vessels (Table I).[9]

Thickening and sclerotic changes are indicated by an increased light reflex, manifested by the copper or silver wire changes, and may coexist with compression changes on the venules by the arteriole when these vessels cross (arteriovenous nicking). This pathologic process involves vascular smooth muscle hypertrophy, leading to fibrosis and hyalinization.[10] In more severe stages of hypertensive retinopathy, retinal vessels become permeable to their intravascular contents as evidenced by retinal hemorrhages and exudates. It is important to recognize that increased hydrostatic capillary pressure cannot develop and lead to exudative reti-

TABLE I. CLASSIFICATION OF HYPERTENSIVE RETINOPATHY

A) Keith-Wagener-Baker Classification:
Group I-tortuosity, minimal constriction
Group II-above changes plus arteriovenous nicking
Group III-above changes plus hemorrhages and exudates
Group IV-papilledema
B) American Ophthalmological Society Committee Classification (Wagener-Clay-Gipner):
1) Generalized arteriolar constriction:
Grade 1-arterioles 3/4 of normal caliber; A/V ratio of 1:2
Grade 2-arterioles 1/2 of normal caliber; A/V ratio of 1:3
Grade 3-arterioles 1/3 of normal caliber; A/V ratio of 1:4
Grade 4-arterioles threadlike or invisible
2) Focal arteriolar constriction or sclerosis:
Grade 1-localized arteriolar narrowing to 2/3 caliber of proximal segment
Grade 2-localized arteriolar narrowing to 1/2 caliber of proximal segment
Grade 3-localized arteriolar narrowing to 1/3 caliber of proximal segment
Grade 4-arterioles invisible beyond focal constriction
3) Generalized sclerosis:
Grade 1-increased light-striping; mild AV nicking
Grade 2-coppery arteriolar color; moderate AV nicking; veins almost completely invisible below arteriolar crossing
Grade 3-silver arteriolar color; severe AV nicking
Grade 4-arterioles visible only as fibrous cords without bloodstreams
4) Hemorrhage and exudates-grades 1 to 4 (based on number of affected quadrants divided by 2)
5) Papilledema-grades 1 to 4 (based on diopters of elevation)

nopathy without a significant increase in venomotor tone coincident with arteriolar constriction. In clinical practice the retinal blood vessels provide a physician with an extremely important index of the status of vascular involvement in hypertensive cardiovascular disease.

The heart. The heart suffers two insults from hypertension. The first is a direct effect of the pressure load imposed upon the myocardium, and results in ventricular hypertrophy. Indirectly, hypertension is a major risk factor for later development of coronary atherosclerosis (ischemic heart disease) and sudden death. On a cellular level the myocardial response to sustained elevated arterial pressure and total peripheral resistance is increased myocardial cell size (i.e., hypertrophy) and a proportionate increase in its vascular supply to adapt to the increased work load. This ventricular hypertrophy is best indexed by an increased RNA production that closely parallels changes in protein and collagen synthesis.[11] Unless adequate treatment is instituted with antihypertensive agents, the hemodynamic sequence associated with this adaptation progresses through the changes of early hypertension, with high cardiac output and ventricular hyperfunction, to later established phases of normal and later reduced

TABLE II. CLASSIFICATION OF HYPERTENSIVE HEART DISEASE

Stage 1	No evidence of cardiac abnormality
Stage 2	Left atrial abnormality
Stage 3	Left ventricular hypertrophy
Stage 4	Congestive heart failure

cardiac output with impaired myocardial performance. These functional alterations may be associated with changes in myocardial composition characterized by increased deposition of collagen and other fibrous tissue components that produce a stiffer and less compliant myocardium with progressively impaired contractility.

Although the myocardium is not as easily inspected as retinal blood vessels, clinical examination and ancillary noninvasive laboratory evaluation provide clinicians with an excellent means to evaluate myocardial size and function. We have established a rather simple and straightforward staging scheme for hypertensive heart disease (Table II).[12] In Stage I hypertensive heart disease the patient has neither chest roentgenographic nor electrocardiographic evidence of any cardiac involvement. Despite the absence of findings, the heart is working against an increased pressure load. With further progression of hypertensive vascular disease and cardiac adaptation, electrocardiographic findings consistent with left atrial enlargement develop,[13] and these are frequently associated with a fourth heart sound (atrial diastolic gallop rhythm) (Table III).[14] These findings characterize Stage II of hypertensive heart disease and reflect changes suggesting that the left ventricle has become less compliant during this early phase of ventricular hypertrophy.[15] Indeed, at the time the atrium is enlarging, myocardial contractility is impaired. These recent studies have demonstrated a significant increase in left ventricular mass and wall thickness associated with decreased ejection fraction and fiber shortening rate.[16]

We have defined Stage III of hypertensive heart disease as manifested by obvious left ventricular hypertrophy in both chest roentgenograms and electrocardiograms (Table III). The Framingham study provided very strong evidence that such patients have greater risk of increased cardiovascular morbidity and mortality when evidence of left ventricular hypertrophy is present.[17] More recent echocardiographic studies have borne out the reliability of these electrocardiographic and roentgenographic criteria in the diagnosis of left ventricular hypertrophy due to hypertension.

TABLE III. DIAGNOSIS OF CARDIAC INVOLVEMENT IN HYPERTENSION

A) Left atrial abnormality (at least two electrocardiographic criteria):
   1) P-wave terminal forces (lead V_1) ≤ -0.04 mm./sec.
   2) Ratio P-wave duration to P-R segment ≥ 1.6 (lead II)
   3) P-wave (lead II) > 0.3 mV
   4) P-wave (lead II) > 0.12 sec.

B) Left ventricular hypertrophy (electrocardiographic criteria used):
   1) Tallest precordial R *plus* deepest precordial S-wave ≥ 4.5 mV
   2) QRS frontal plane axis $< -30°$
   3) T-wave axis $\geq 180°$ from QRS axis (LV strain)

C) Left ventricular hypertrophy (roentgenographic):
   1) Ungerleider index $\geq 10\%$ plus two electrocardiographic criteria
   2) Or Ungerleider index $\geq 15\%$

D) Echocardiographic (M-mode) criteria (see Figure 1):
   1) Anatomical:
      a) Left atrial enlargement: > 4.0 cm or ≥ 2.0 cm./m.^{2}
      b) Left ventricular hypertrophy: septal and/or posterior wall thickness ≥ 1.1 cm.
      c) Left ventricular mass:
      $(LVID_D + IVS+LVPW)^3 - (LVID_D^3) \times 1.05 \geq 140$ gm./m.^{2}

   2) Functional:
      a) Ejection fraction: $\geq 55\%$

$$\frac{\text{(End-diastolic volume)-(End-systolic volume)}}{\text{End-diastolic volume}} \times 100\%$$

      b) Fractional shortening of minor axis: $\geq 30\%$

$$\frac{LVID_D - LVID_S}{LVID_D} \times 100\%$$

      c) Fiber shortening velocity (V_{cf}): ≥ 0.9

$$\frac{LVID_D - LVID_S}{LVID_D \times \text{Ejection Time}}$$

Although not all patients with ventricular enlargement have diagnosed left ventricular hypertrophy by our criteria, by choice, fewer patients will be given a "false positive" diagnosis of cardiac enlargement.

The final, and perhaps most obvious, stage of hypertensive heart disease is that of frank congestive heart failure (Stage IV). Cardiac failure from hypertensive heart disease is clinically very similar to that caused by any other factor predisposing to left ventricular decompensation, except that it is engendered by a long-standing pressure overload. Indeed, hypertension is the most common cause of cardiac failure in this country. The second most common is coronary arterial disease associated with hypertension.[18]

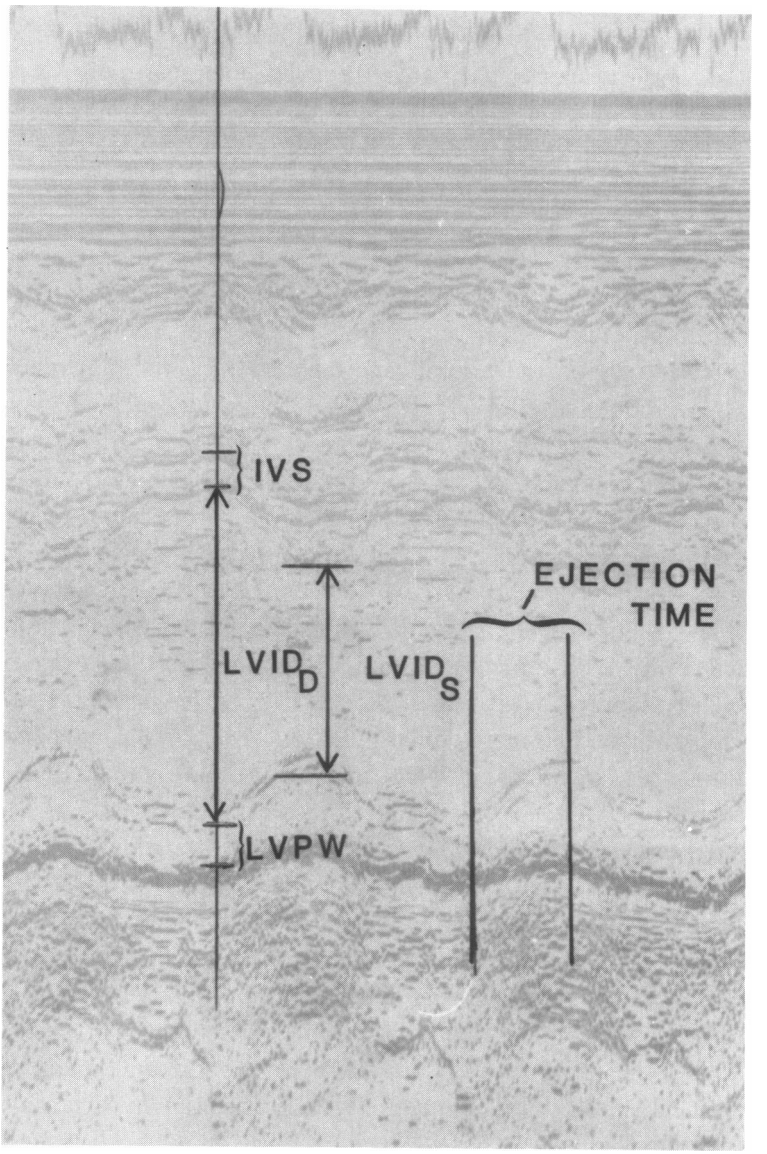
Coexistence of coronary artery disease (atherosclerotic or ischemic heart disease) and hypertension is a well-known clinical entity. Heart weight and diameter of the coronary arteries are related linearly until the heart weighs approximately 500 g., after which coronary arterial diameter does not increase proportionately. As the heart enlarges, more oxygen is required, demanding greater blood supply. If this supply is inadequate to meet oxygen demand, even without reduction in coronary arterial lumina, angina pectoris can develop. The major determinants of myocardial oxygen demand are ventricular chamber diameter, ventricular (systolic) pressure, and wall thickness. Each variable increases as hypertensive vascular disease and its pathophysiological hallmark, ever-increasing total peripheral resistance, progress.

Kidney. Pathologic studies indicate that primary renal parenchymal diseases can produce arterial hypertension through two mechanisms: progressive renal arteriolar changes associated with ischemia and progressive destruction of renal parenchyma that impairs renal excretory ability.

Current concepts of essential (or primary) hypertension regard the kidney as the recipient rather than the cause of the hypertension. Large renal arteries usually are normal, particularly early in the course of the disease; but smaller arteries have changes of arteriosclerosis as manifested by intimal fibrosis, hyalinization, and thickening with splitting of the internal elastic lamina. With time, vascular disease progresses in severity as does impairment of renal tubular function. First, renal concentrating ability diminishes, then other tubular functions become impaired. Eventually, glomeruli become involved and filtration capacity falls.

Currently, early assessment of renal involvement in patients with hypertension or nephrosclerosis is indirect and at best unsatisfactory. Noninvasive assessments of renal function are useful in measuring sequential changes in renal integrity. Endogenous creatinine clearance, protein excretion, and concentrating ability are a few of the clinically useful means available to monitor renal functional changes in essential hypertension. Renal biopsy, the most definitive assessment of structural integrity, has limited clinical applicability in patients with essential hypertension (for obvious reasons).

Recently, we have shown a very strong correlation between the level of serum uric acid and total peripheral and renovascular resistance and a fall in renal blood flow.[20] While arterial pressures and glomerular filtration rates were similar in these uncomplicated essential hypertensive patients



Echocardiogram of left ventricular cavity, below the level of the mitral valve. IVS = interventricular septum, $LVID_D$ = left ventricular internal diameter in diastole, $LVID_S$ = left ventricular internal diameter in systole, LVPW = left ventricular posterior wall (see Table III)

with low (≤5.9 mg./dl.), normal (6.0-8.9 mg./dl.), and high (9.0-11.4 mg./dl.) serum uric acid levels, their total peripheral and renovascular resistance rose in proportion with the uric acid concentration as renal blood flow decreased. Moreover, even in those patients with similar arterial pressures and no evidence of cardiac involvement, plasma volume progressively contracted as uric acid levels rose. These new data suggest that serum uric acid levels may reflect early renal vascular involvement in these patients with untreated essential hypertension because the excreted uric acid load depends upon the glomerular filtration rate and tubular absorption and secretion—all functions dependent upon renal blood flow. These findings must be studied in further detail to understand more completely their full pathophysiologic significance. Eventually, as renal parenchymal function becomes further impaired, creatinine clearance and serum creatinine and blood urea nitrogen concentrations rise to reflect diminishing excretory performance.

Conclusion

Essential hypertension is a hemodynamic disorder that affects the entire systemic vasculature; it is manifested by a progressive rise in arterial pressure that reflects a continuous increase in vascular resistance as long as a patient remains untreated. Specific means for clinical and laboratory assessment of the major target organs of hypertension are improving. Most of these means provide clinical indices related to the pathophysiologic changes. In particular, we can now demonstrate the severity of the degree of vasoconstriction by history, physical examination, and routine laboratory means. Vascular constriction can be seen in the degree of hypertensive retinopathy. Early cardiac changes reflecting left ventricular hypertrophy can be documented by electrocardiographic and echocardiographic changes. Serum uric acid concentration may represent an early index of intrarenal vasoconstriction even before creatinine clearance and serum creatinine content change. Having recognized these changes, the physician can minimize progression of vascular and functional impairment of the target organs through effective antihypertensive drug therapy.

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